Interview: Dr. Simon Gregory

Genetic Research On Pediatric Chiari

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This month we continue our focus on the recent recipients of Conquer Chiari Research Grants and profile Dr. Simon Gregory, a genetic researcher at Duke University...

How did you get interested in researching Chiari?
The study of Chiari was a particular passion of Dr Marcy Speer, a close friend and colleague. Together with my fellow faculty member at the Duke Center for Human Genetics, Dr. Allison Ashley-Koch, we decided to maintain Marcy's passion for studying the disorder after Marcy lost her battle with breast cancer.

What do we currently know about the genetics of Chiari?
We don't currently know a lot about the genetics of Chiari. A genetic component in at least a subset of nonsyndromic CMI cases is supported by the fact that identical twins are more likely to both be affected than non-identical twins, the presence of multiple affected CMI members in families, and the fact that CMI co-occurs with other known genetic diseases. In addition, previous genetic studies by our group have already identified significant evidence for linkage of Chiari type I on chromosome 9 and 15.

Some researchers (such as Koentges) are focusing on signaling pathways. Can you explain the difference between genetic coding which could lead to Chiari and problems with signaling pathways which could lead to Chiari?
One approach ("genetic coding") to the study of CMI is to look at CMI families containing multiple affected individuals and identify regions of the genome that are shared among affected individuals. A variety of approaches can then be used to narrow the regions of interest with the eventual goal of identifying genes involved in the disease. Another approach ("signaling pathways") is to use prior information about the disease mechanism and identify genes/pathways that are important at those stages in development.

Focusing on the size of the posterior fossa has led some to describe Chiari as a defect involving the mesoderm. What is the mesoderm?
The mesoderm is one of three primary germ layers. It's responsible for the formation of cartilage, bone, connective tissue, dermis, etc. During development, the mesoderm develops into several different subtypes, including the paraxial mesoderm. CMI has been suggested to be due to an underdeveloped occipital bone that results from a defect originating from the paraxial mesoderm.

How important is it to classify Chiari in such a way (meaning mesodermal defect)?
It depends on the approach used. For our approach, it is not that important initially to classify Chiari as a mesodermal defect since we are scanning the entire genome and do not rely on prior information about the disease. However, once we locate regions of the genome that likely harbor the disease gene or genes it is useful to have an understanding of the disease mechanism in order to prioritize candidates for follow-up studies.

Based on what you have learned so far, what percent of Chiari cases do you think are heritable versus isolated?
Genetic studies thus far have focused only on a small subset of nonsyndromic CMI patients, so it is hard to say what percentage of all CMI cases are heritable. In addition, we still don't have a good sense of the prevalence of CMI due to an undetermined number of asymptomatic patients - we are hoping that our additional NIH funded CMI grant will begin to answer these questions.

If someone has isolated Chiari, do you think their children are at higher risk for developing Chiari symptoms?
It is possible, but we don't have the data yet to be able to say one way or another.

Can you explain the Conquer Chiari project you will undertake.
We will collect blood and tissue samples from CMI pediatric patients undergoing decompression surgery for the analysis of whole genome expression (measuring gene activity levels across the genome). Expression patterns will be used to identify subtypes of CMI patients. We will then identify combinations of clinical and radiological predictors for each subtype, and genes/regulatory pathways that differentiate these subtypes.

How will this impact patients?
A lot of variation exists in terms of the presentation of CMI. Our goals are to more accurately identify CMI subtypes and to gain a better understanding of the molecular basis of these subtypes. Our hope is that this study will lead to future studies which will result in a more patient-specific approach to treatment.

What do you think we will know about the genetics of Chiari in 20 years?
Hopefully we will have a better understanding of the number and types of genes that play a role in the development of CMI, and to determine if individuals are going to develop CMI using their genetic code in combination with environmental influences.